Dissertation on

CLINICAL FEATURES OF TYPE 1 DIABETES MELLITUS AND PREVALENCE OF ITS COMPLICATIONS

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CERTIFICATE

This is to certify that the dissertation titled **"CLINICAL FEATURES OF TYPE 1 DIABETES MELLITUS AND PREVALENCE OF ITS COMPLICATIONS"** is the original work done by **Dr.M.RAJKUMAR,** Postgraduate in Institute of Internal Medicine, Madras Medical College, Government General Hospital, Chennai - 600 003 to be submitted to The Tamilnadu Dr.M.G.R. Medical University, Chennai - 600 032, towards the partial fulfillment of the requirement for the award of M.D. Degree in Internal Medicine, March 2007.

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DECLARATION

I, Solemnly declare that this dissertation entitled **"CLINICAL FEATURES OF TYPE 1 DIABETES MELLITUS AND PREVALENCE OF ITS COMPLICATIONS"** was done by me at Madras Medical College and Government General Hospital during 2004 - 2007 under the guidance and supervision of **Prof.K.RAGHAVAN**. This dissertation is submitted to the Tamilnadu Dr.M.G.R. Medical University, towards the partial fulfillment of requirements for the award of M.D. Degree in General Medicine, Branch - I.

Place :

Date :

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CONTENTS

INTRODUCTION

Diabetes mellitus is a clinical syndrome characterised by hypgerlycemia due to absolute or relative deficiency of insulin. Lack of insulin affects the metabolism of carbohydrate, fat and protein, and causes significant disturbance in water and electrolyte homeostasis. Long standing metabolic derangements is frequently associated with permanent and irreversible functional and structural changes in the cells of the body, the vascular system being particularly susceptible.

Although type I diabetes has a much lower world wide incidence then type 2 diabetes, the loss of quality life for those with type I diabetes in especially great due to earlier onset and greater degree of glycaemic exposure.

Type I diabetes carries a substantial risk of morbidity and early mortality due to its complications which are numerous and affects both the macro and microvasculature.

Macrovascular complications result from accelerated atherosclerosis, leading to early mortality as well as non fatal myocardial infarction, peripheral vascular disease and ischemic stroke.

The microvascular complications also contribute to diabetic mortality through nephropathy, renal failure and further contribute to burden associated with diabetes in the form of (retinopathy) blindness, neuropathy, lower extremity infection and amputation.

While the microvascular disease is specific of diabetes the macrovascular disease is not threshold specific but get accelerated.

The acute complications are hypoglycemia, hyperglycemic emergencies and infections.

Extensive data are available on the occurrence of type 1 diabetes mellitus in globally diverse population, and little is known about the geographic variation in the complication rates.

This study has tried to find out the clinical features and presentations at the time of diagnosis, the prevalence of complication in type 1 diabetes mellitus both microvascular and macro vascular, the association of duration of diabetes with its complications.

REVIEW OF LITERATURE

Sushrutha and Charaka the Indian Physicians during the 5th and 6th century AD were the First to recognise diabetes mellitus by the swectness of the urine, Aretaeus was the 1st to use the term diabetes. Thomas willis described it as the pissing evil.

Type I diabetes is not the common form of diabetes. Type 2 diabetes is 10 times more common than the type 1 diabetes. Type 1 accounts for only 5 - 10% of all diabetic population[1].

The peak incidence of diabetes type 1 is between 10-14 years of age. The incidence of type 1 diabetes in USA for those under the age of 20 years is 13/100 000/yr and in the adult it is around 16/100 00 / year.

Data collected from different part of India reveal, incidence of type 1 diabetes below 15 years of age to be 1-4% of all diabetics. As per Madras type 1 diabetes mellitus registry group of 1995 the incidence of type 1 diabetes was 10,5/100000 children with higher incidence in boys as in study showed by Ramachandran, Snehalatha Krishnaswami.

The overall prevalence of diabetes mellitus in India is 1-2%. The prevalence at type I is largely unknown Patel[5] et al., and Gupta have shown type I is uncommon in North India. Krishnaswamy et al., and Chandra et al.,[6] reported the prevalence of jeuvenile diabetes in South India as 0.8% of all diabetics.

In a study done at Govt. Childrens Hospital, Egmore, during 1977 - 1982 by TK Sengottuvel et al., the incidence was 22.8 / 100 000 out patient cases.

Prof. Seshiah's incidence was 160 / 100 000.

In central Kerala it was 3.61 among diabetics.

The prevalence of type 1 diabetes has been increasing in recent decades, upto twice the frequency every 10 years in some countries. The annual rate of increase in type 1 diabetes in European children under 15 years of age for 1989 - 94 was estimated a 3.4%[2]. This trend varies from country to country. The annual incidence ranged from 3.2 to 40.2 per 100 000 in one report.

The empiric risk of developing type 1 diabetes in a general population is 0.4%. The risk of developing type 1 diabetes mellitus in the off spring of a diabetic father is 6.1%, in the offspring of a diabetic mother it is 2%, in the offspring of a diabetic father and mother is 3.6%. In a monozygotic twin the risk is 30 - 50% in a dizyogtic twin it is 5%. Approximately 1 in 20 first degree relatives of patients with type 1 diabetes mellitus will develop this disorder.

CLASSIFICATION[3]

Etiological classification of diabetes mellitus

Type 1 diabetes

β-cell destruction, usually leading to absolute insulin deficiency.

A. Immune mediated

B. Idiopathic

Type II diabetes

May range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretary detect with or without insulin resistance.

III. Other specific types of diabetes

a. Genetic defect of β cell function characterised by mutation in various genes.

b. Genetic defects in insulin action

c. Disease of exocrine pancreas

d. Endocrinopathies

e. Chemical or drug induced

f. Infection

g. Immune mediated (uncommon)

h. Other genetic syndromes associated with diabetes mellitus.

IV. Gestational diabetes mellitus

Diagnostic criteria[4]

Three ways to diagnose diabetes are possible, and each in the absence of unequivocal hyperglycemia, must be confirmed on a subsequent day, by any one of the three methods.

1. Symptoms of diabetes plus or casual plasma glucose concentration ≥ 200 mg/dl.

Casual is defined as any time of the day, without regard to time since last meal. The classic symptom of diabetes include polyuria, polydipsia and unexplained weight loss.

(or)

Fasting plasma glucose ≥ 126 mg/dl (7.0 m.mol / lit) fasting is defined as no caloric intake for at least 8 hrs.

2 hours post glucose load ≥ 200 mg/dl 11.1 m.mol / lit during an OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 gm anhydrous glucose dissolved in water.

It is differentiated from type 2 DM by the presence of the following given feature in type 1 DM.

- Commonly develops before the age of 30
- Lean body habitus
- Propensity to develop ketosis
- An increased risk of auto immune disorder such as:

    Auto immune thyroid disease

    Perinicious Anaemia

    Vitiligo

    Addison's. disease

Aetiology and risk factor for development of type I DM.

Type 1DM is influenced by genetic and environmental factors. Type I DM is a T-cell mediated autoimmune disease, targets include insulin and glutamic acid decarboxylase. Over 95% of caucasian type I DM subjects carry HLA DR3 or DR4 antigens.

Genetic predisposition is thought to be crucial for the development of the autoimmune form of type 1 diabetes.

In a recent European (EURODIAB) survey, the risk for a type 1 DM mother having a child with onset of diabetes before the age of 5 years was 1.8% and for father 3.4%[7].

This means that in more than 90% of cases in which type I diabetes is diagnosed there is no other known case in the family history and these figures are reassuring to most diabetic people wanting to have children.

The HLA grouping of the children along with determination of anti islet and antiinsulin antibody can help greatly in predicting the risk of type 1 DM siblings[8].

Prevalence of islet cell antibody appears to be low in South India type 1 diabetic population[9].

Likely environmental triggers in genetically susceptible individuals include viruses and chemical toxins.

Viruses - coxsackie B4, Rubella, Mumps and Echovirus[10].

Exposure in pregnant women to nitrosoamines in smoked meat increases the risk in

children.

Clinical Features

Type 1DM is diagnosed during sudden appearance of weight loss 1 to 2 kg/week accompanied by polyuria, nocturia and polydipsia in young lean subject, fatigue in later part of the day is always present, appetite is good or even increased. A noticeable muscular atrophy is particularly visible in the thighs.

In the presence of ketosis smell of acetone in the breath may be noticed.

If the 1st time of visit reveals massive glucosuria, moderate to intense ketonuria and high blood glucose level > 270 mgm/dl, insulin therapy should be started on the same day.

Determination of antiislet autoantibodies allow clear identification of the two other forms of type 1 diabetes, the preclinical phase of type 1 autoimmune diabetes in the young and LADA.

TREATMENT

Treatment of uncomplicated type I DM classically rests on a tripod, insulin, diet and physical activity coherently balanced with the help of a platform of knowledge and controlled by frequent blood glucose monitoring, if one leg of tripod falls the equilibrium fails.

Insulin replacement is clearly the most important part of treatment, it is based on mimicking the non - diabetic insulin secretion pattern, with its slow basal delivery throughout the entire day and boosts at the meal time.

Rapid acting insulin is injected before meals to simulate postprandial insulin secretion and intermediate or long acting insulin is injected once or twice daily to simulate basal delivery.

DIET

The approaches to nutrition of type 1 diabetes have radically changed in recent decades, more emphasis in put on the role of a well balanced, healthy, varied diet, rich in complex carbohydrates with a low glycemic index and high in fibre with shift from saturated to polyunsaturated to monounsaturated fats, a certain amount of sucrose is permitted.

Ideally the patient should match the dose of preprandial insulin to the size and content of meals expected to follow (Carbohydrate counting).

Physical exercise and sports at least in young adults are needed more for overall health maintenance and physical and mental balance rather than for obtaining good blood glucose control.

Blood glucose self monitoring has been one other most important steps in the process of patient empowerment in relation to the disease.

Patient education : The patient should be clearly informed in writing using a (therapeutic contract) that defines and agrees the desirable goal of treatment, one of the most challenging aspects is to encourage patient to stop smoking.

Acute Complications

Hypoglycemia is the main concern and burden in life of all type 1 diabetic patients and

main obstacle to obtaining very good metabolic control, clinical manifestations are due to catecholomine release or CNS manifestation.

Adrenergic symptoms like perspiration, tachycardia, tremor, pallor and uneasiness occurs earlier, CNS manifestations include change in personality, behaviour, confusion, obtundation, convulsion and coma, nocturnal hypoglycemia may be manifested by nightmares, night sweats and morning head ache.

In patient on insulin treatment[11] in type 1DM insulin levels cannot decrease with exercise or fasting, in Type 1 DM more than 2 years duration the glucogon response to insulin induced hypoglycemia is usually reduced and after 15 years of diabetes the catecholamine response may wane leaving the patient defenceless against hypoglycemia[12].

Diabetic Ketoacidosis

Pathophysiology[13]

- Increased glycogenolysis and gluconeogenesis in the liver and kidney resulting in marked hyperglycemia.
- Insulin lack and counter regulatory hormone excess activate the hormone sensitive lipase leading to lipolysis, the FFA thus released are taken to liver and serve as substrate for ketogenesis..
- Low insulin and high glucogen level in DKA result in low malonyl CoA production by the hepatocytes leading to reduced entry of FFA into mitochondria.
- The end result is rapid increase in β hydroxybutyrate and acetone.

- Brain and skeletal muscles can metabolise ketone bodies normally, but it is impaired in DKA.

- Acetoacetate and β hudroxy butyrate are strong acids and are fully associated at body pH consuming body buffers and resulting in acidosis.

- Marked hyperglycemia causes osmotic diuresis, increased extracellular osmolarity shifting water from cells leading to cellular dehydration.

Biochemical Mechanism of diabetic tissue damage

Chronic tissue damage is related to severity and duration of hyperglycemia, tissue damage may continue to evolve even after hyperglycemia has been improved (hyperglycemic memory)[14].

At cellular level hyperglycemia may damage tissue by :

- Enhanced glucose flux through the polyol pathway

- Formation of advanced glycation end products.

- Activation of protein kinase C.

- Stimulation of hexosamine pathway.

Excess mitochondrial production of reactive oxygen species and superoxide may also play a role.

Diabetic Retinopathy

Earliest sign of retinopathy is basement membrane thickening, Type IV collagen and laminin increases while heparensulphate and proteoglycan decreases[6].

Pericyte loss is another feature of retinopathy.

There is increased capillary permeability and leakage resulting in extravasation of products from circulation. The resulting mass of fibrinoid material and dying lipid laden macrophages are seen as hard exudates in fundoscopy.

Diabetic Retinopathy is a highly specific vascular complication of diabetes, the prevalence is strongly associated with duration of illness. After 20 years of diabetes nearly all patients with type 1 diabetes and >60% of type 2 diabetes have some degree of retinopathy[16].

In the WINCOMIN Epidemiological study of diabetic retinopathy WESDR 3.6% of type 1 and 1.6% of type 2 patients were legally blind[17]. Vision threatening retinopathy virtually never appears in type 1 diabetes in the first 3 - 5 years of diabetes or before puberty.

For clinical purpose retinopathy is divided into three major groups.

1. Background retinopathy
2. Preproliferative retinopathy
3. Proliferative retinopathy

Back ground retinopathy

Micro aneurysm is the earliest evidence in about 25% of patients. Micro aneurysm of retinal capillaries are thought to develop subsequent to loss of supporting pericytes around the capillary wall. Other features include tortuosity of vessels, linear flame shaped retinal haemorhages, hard exudate, cotton wool spots.

Preproliferative retinopathy has multiple micro aneurysm and cotton wool spots along with IRMA ie intra retinal microvascular abnormality.

Proliferative retinopathy

Hallmark of this stage is neovascularisation New vessels may arise on the optic disc or on retinal surface unsupported by connective tissue. Other features include glial proliferation, vitreous hemorrhage and retinal detachment.

Diabetic retinopathy primarily affects veins, venules and venous end of capillaries.

Other eye complication are cataract and rubeosis iridis.

In type 1 diabetes, suggested screening schedule for retinopathy are as follows[18]. Need for screening is irrefutable.

First examination within 3 - 5 years after diagnosis of diabetes, once the patient is 10 years or older, minimum routine follow up yearly once.

DIABETIC NEUROPATHY

The pathogenesis and progression of diabetic peripheral neuropathy are related to the duration and severity of hyperglycemia. Glucose could damage nerve cells via increased glucose flux through polyol pathway, non enzymatic glycation of proteins and other longlived macro molecules and oxidative stress.

Pathological features include distal fibres loss and demyelination with slowing of conduction velocity which is initially reversible on correction of hyperglycemia. Myelinated fibres may be relatively protected, longest axon may be most affected.

In Europe and North America neuropathy occurs in approximately 20%[19] individuals with long standing diabetes. It may manifest as polyneuropathy mononeuropathy and / or autonomic neuropathy.

Mononeuropathies may involve cranial, truncal or peripheral nerves, cranial mononeuropathy commonly involve oculomotor nerve with characteristic pupillary sparing, sixth and seventh cranial nerve palsies may also occur.

Truncal mononeuropathy occurs with sudden onset of pain with hyperaesthesia in a unilateral radicular distribution, thoracic and upper lumbar segments, which may mimic root pain of herpes zoster.

Peripheral monopeuropathy may present with carpal tunnel syndrome or peroneal neuropathy producing sudden painless footdrop.

Most common form of polyneuropathy is distal symmetrical polyneuropathy. It presents with distal sensory impairment loss of ankle reflex and abnormal position and vibration sense.

Proximal motor neuropathy ie diabetic amyotrophy is more common in type 2 DM.

Neuropathy may selectively involve small fibres causing pseudo syringomyelia or large fibres causing pseudotabes.

Autonomic neuropathy can be detected by simple clinical tests for cardiovascular reflex like change in heart rate during deep breathing, standing, valsalva and blood pressure response to standing and sustained hand grip, patients with autonomic neuropathy are prone for sudden death from painless myocardial infarction.

DIABETIC NEPHROPATHY

The pathology of diabetic kidney affects both the glomerulus and tubular interstitium. Glomerular enlargement occurs initially increased capillary length and increased filtration surface area, followed by basement membrane thickening and mesangial expansion.

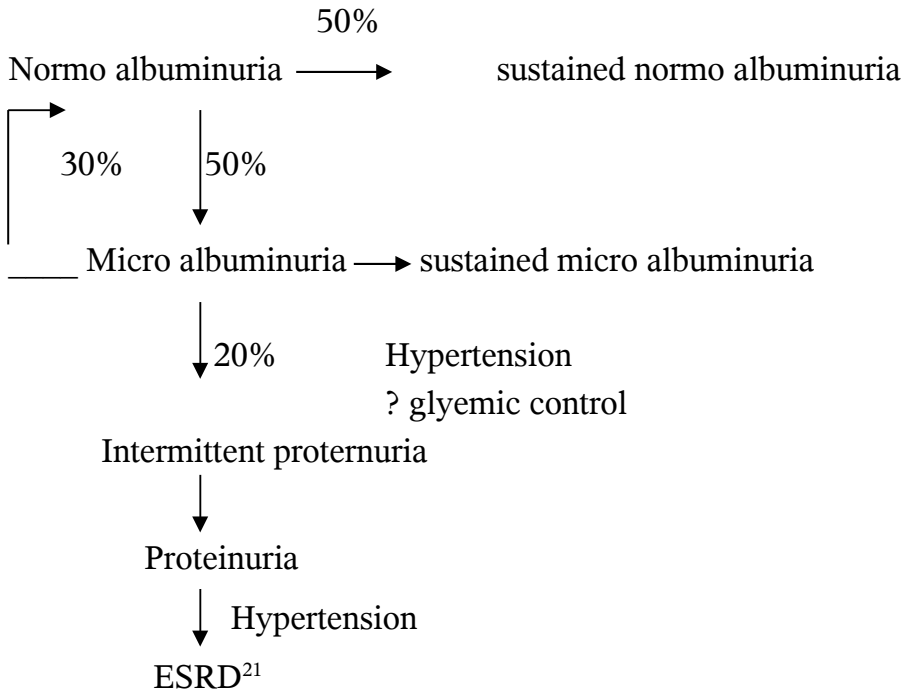
At the time of diagnosis both glomerular and kidney volume are increased[20] . Diabetes is the single most common cause for end stage renal disease.

About 20 - 30% patients with type 1 diabetes develop evidence of nephropathy. The earliest clinical manitestation is low but abnormal level of albumin in urine called micro-albuminuria (30-300 mg/day or 20 μg/mt). Patients with micro albuminuria are referred to as having incipient nephropathy.

Without specific intervention 80% of subjects with type 1 diabetes who develop sustained microalbuminuria have their urinary albumin excretion increase at a rate of 10 - 20% per year to the stage of overt nephropathy or clinical albuminuria (≥ 300 mg/24 hrs or ≥200 μg/ml) over a period of 10 - 15 years with hypertension also developing along the way.

Once overt nephropathy occurs without specific interventions, the glomerular filtration rate gradually falls over a period of several years at a rate that is highly variable from individual to individual.

ESRD develops in 50% of type 1 diabetic individual with overt nephropathy with in 10 years and > 75% by 20 years.



	24 hrs	Timed collection	Spot collection
Normal	< 30 mg/24 hr	< 20 µg/mt	< 30 µg/mg of cr.
Micro albuminuria	30 - 300 mg/24 hr	20 - 200 µg/mt	30 - 300 µg/mg of cr.
Clinical albuminuria	> 300 mg/24 hr	> 200 µg/mt	> 300 µg/mg of cr.

Because of variability of urine albumin excretion 2 or 3 specimen collected within 3 - 6 month period should be abnormal before considering a patient to have crossed one of these diagnostic thresholds.

Management includes, tight glycemic control, hypertension control, ACE inhibitors and protein restriction. These measures play a major role in delaying ESRD. Living Donor (related) renal transplant is now gold standard of treatment.

MACROVASCULAR COMPLICATIONS

Lipid Alteration

Patient with well controlled type 1 diabetes and normal triglyceride level develop increased level of chylomicrons and very low density lipoprotein (VLDL) during insulin deficiency[22].

Two mechanism may play role

1. Decreased level of Lipoprotein lipase with insulin deficiency produce a defect in lipolysis of triglyceride rich lipoproteins.

2. Increased level of Free fatty acids provide substrate for over production of hepatic VLDL. Insulin therapy reverses both these defects and restores triglyceride level to normal.

LDL (low density lipoprotein) level may be elevated in type 1 diabetes. This may be due to insulin deficiency causing reduced activity of LDL receptors impairing its clearance. The glycation and oxidation of LDL reduce its affinity for its receptors. Insulin therapy revert this to normal. Poorly controlled type 1 diabetes leads to increased lipolysis and over production of non esterified tatty acids (NEFA) and decrease activity of lipoprotein lipase, the insulin dependent enzyme that hydrolyses triglyceride in circulating lipoprotein.

The result is hyper triglyceridemia severe enough to cause pancreatitis, eruptive xanthoma, lipaemia retinalis. Lipid profile is nearly normal in well controlled type 1 DM.

Hypertension - It is twice as common in diabetic as in general population[22].

In type 2DM there is associated obesity, insulin resistance and other features of metabolic syndrome. In type 1 diabetes in microalbuminuria phase of diabetic nephropathy blood pressure rises, total body Na^+ and peripheral resistance are raised. Hypertension worsens both macro vascular and micro vascular complications.

Effective treatment of blood pressure reduces microvascular notably, nephropathy and certain macrovascular events and diabetes related deaths.

CARDIOVASCULAR DISEASES

Both type 1 and type 2 diabetes increases cardiovascular risk 2 - 4 folds compared with general population. Cardiovascular disease kills 75% of all diabetic people and accounting for 36% of all deaths in myocardial infarction.

The pathology is intimal thickening with atheroma formation; endothelial disease may cause increased adhesiveness. Impaired relaxation due to decrease NO production. Advanced glycation end products and impaired compliance also play a role.

Atheroma formed in diabetes has certain special characters it is more extensive, diffuse and involves distal vessels[23].

Coronary artery disease and hypertension can account for most myocardial abnormalities in diabetes, postmortem studies showed evidence of specific cardiomyopathy in the absence of coronary artery atheroma.

Increased LDL predisoposes to CAD[24].

Clinical manifestation of cardiovascular disease are angina, myocardial infarction, heart failure, dysrrythmia, peripheral and cerebrovascular disease.

Primary prevention of cardiovascular disease and risk factor management

- Life style management, cessation of smoking, optimizing glycemic control, management of dyslipidemia, management of hypertension and renoprotection.

Diabetes and tuberculosis[25]

Tuberculosis has higher incidence in diabetes. Involvement of lower lobe is common, bilateral involvement may also occur. Diabetes reactivates latent tuberculosis. Chest radiography should be taken once in 6 months in all diabetic patients. Tuberculosis must be suspected if there is an increase in insulin requirement, associated with weight loss.

DIABETES AND PREGNANCY

Normal pregnancy itself produces few alteration in glucose metabolism[26]. In the early weaks of pregnancy serum level of estrogen and progestorone raise and induce β cell hyperplasia, resulting in increased elaboration of insulin and heightened sensitivity to insulin causing low fasting blood sugar. In the later half of pregnancy facilitated insulin action continues and at the same there is increased elaboration of counter hormones, human placental lactogen, prolactin, and cortisol, results in insulin resistance and stress on carbohydrate metabolism and hence the gestational diabetes develop in later half of pregnancy.

Poorly controlled diabetes before conception and during first trimester of pregnancy can cause major birth defect in 5% to 10% of pregnancies and spontaneous abortion in 15 to 20% of pregnancies.

Poorly controlled diabetes during second and third trimester of pregnancy can result in excessively large babies posing risk to both mother and child.

PREVENTING DIABETIC COMPLICATION

Uncontrolled diabetes can lead to serious complications such as heart disease, blindness, kidney damage and lower limb amputation. Working together, people with diabetes and their

health care providers can reduce the occurrence of these and other diabetes complications by controlling the level of blood glucose, blood pressure and lipids and by receiving other preventive care practices in a timely manner.

Glucose Control : Improved glycemic control benefits people with both type of diabetes. Every one percentage drop in Hb AIc reduces risk of microvascular complication by 40%.

Blood pressure control reduces risk of cardiovascular disease in a diabetics by 33 - 50% and risk of microvascular complication by 33%.

Improved - control of cholesterol can reduce cardiovascular complications by 20% to 50%.

SCREENING FOR DIABETICS[27]

Most cases of type 1 diabetes are detected after development of symptoms. widespread clinical testing of asymptomatic individuals for the presence of auto antibodies related to type I diabetes cannot be recommended at this time as means to identify person at risk. The reasons for this include

1. Cutoff values for some of the immune marker assay have not been completely established in clinical setting,

2. There is no consensus as to the action that should be taken when a positive antibody result is not obtained

3. Incidence of type 1 diabetes is low and testing of healthy children identify only a very small number (< 0.5%) who at the moment may be prediabetic.

AIMS AND OBJECTIVES OF THE STUDY

To describe the prevalence of microvascular and macrovascular complications of type 1 diabetes mellitus assessed by both reported and measured disease risk factors.

- To study the clinical features and presentation of type 1 diabetes mellitus.
- To analyse the association of duration of illness with its complications.

MATERIALS AND METHODS

SETTING

Out patient clinic in the Department of General Medicine and Department of Diabetology, Madras Medical College and Government General Hospital, Chennai - 3.

It is a single centre cross sectional study of randomly selected patients with type 1 diabetes mellitus.

Period of Study : August 2005 to July 2006

Twelve months duration

150 Randomly selected patients with type 1 diabetes mellitus attending the out patient clinic formed the material for the study.

Inclusion Criteria

1. Patient with diabetes mellitus with onset of disease at or below the age of 25.

    - Requirement of insulin as the initial mode of treatment at the time of diagnosis of diabetes.

    - A member of defined community.

EXCLUSION CRITERIA

Patient of age more than 25 even if they require insulin as a mode of treatment initally who may belong to LADA Late Onset diabetes in adults.

The patient were subjected to detailed questioning which included, history of the physician diagnosed complications. Health care behaviour, which included blood glucose testing, insulin administration, of number of visit to physician etc. Patient was asked about smoking status, educational and occupational history, medication and insulin use, alcohol consumption and family history of diabetes. Examination consists of procedure which includes sitting blood pressure measurement with a random zero sphygomomanometer. Following HDFP protocol [Hypertension detection and follow up program] with systolic and diastolic pressure $\geq$ 140 and 90 mmHg respectively, or treatment with antihypertensive drugs were considered positive for hypertension. Height and weight were recorded in centimeters and weight respectively.

Detailed cardiovascular and neurological histories were taken to supplement the self reported data, cardiovascular examination were done, recording the presence of ankle edema, basal crepitations and peripheral pulses. Electrocardiogram was done and echocardiogram was done whenever necessary.

MNSI Michigan neuropathy screening instrument examination, questionnaire was used for testing clinical neurology. Neurological examination were done by eliciting the deep tendon reflexes, vibration perception at the bony prominence, sensory testing was done using a pin. Seven correct answers out of ten were considered normal, one to six correct responses were

considered as reduced sensation and no correct response was considered as absent sensation.

Visual acquity was measured by using vision card and number of letter size were recorded for both eyes. Fundoscopy examination was done to look for the presence of any signs of retinopathy.

LABORATORY ANALYSIS

Both a fasting and post prandial blood glucose level were tested. A non timed urine sample was taken, and tested for albumin sugar and deposits. Microalbuminuria test was done using the (micral) disptick testing method.

Renal function tests which included the electrolytes were done on all patients. A fasting lipid profile was tested, high level of cholesterol and / or triglyceride levels were considered as abnormal.

Glycemic control was assessed using the measurement of glycosylated hemoglobin $HbA1_c$. In a normal person the value is 3 - 6%.

DEFINITION OF END POINTS

Reported complications were defined as a self report of physician diagnosis including retinopathy and laser treatment, neuropathy, kidney problems related to diabetes and / or albumin in the urine, high cholesterol and / or triglycerides.

Mascrovascular compliactions including myocardial infarction, stroke, peripheral vascular disease angina and amputation. MNSI questionnaire was used as a marker for neuropathy, which consisted of 15 Yes or no questions. Possibility of neuropathy was done by using bed side examinations. Microalbuminuria was tested using micral dipstick testing method.

Glycemic control

Patients who had HbA1c less than 7% were considered as are with good glycemic control.

7 - 8% under moderate control.

> 8% had poor control with treatment action immediately.

Hypertension was defined in my study as systolic pressure $\geq$ 140 mmHg and ddiastolic pressure $\geq$ 90 mmHg, or patient is on antihypertensive medication.

RESULTS

AGE DISTRIBUTION

The age of patient selected for the study, 150 in number ranged from 10 years to 41 years.

Table 1 shows the stratified age distribution of the patients studied.

TABLE : 1

Age of the patient	No. of patients	Percentage
≤ 15 years	22	16%
16-25 years	67	45%
26-35 years	43	27%
≥ 36 years	18	12%

GENDER DISTRIBUTION

Gender distribution of the 150 patients selected randomly for the study 82 were females and the remaining 68 males.

TABLE : 2
SHOWS GENDER DISTRIBUTION

Sex	No. of patients	Percentage
Male	68	45%
Female	82	55%

AGE AT DIAGNOSIS

Age of the patient at the time of diagnosis of dilates mellitus ranged from Table 3 shows the age wise distribution at the time of diagnosis.

TABLE : 3

Age at diagnosis	No. of patients	Percentage
≤ 10	19	13%
11-15	64	42%
16-20	51	34%
> 20	16	16%

DURATION OF DISEASE

Duration of diahetes mellitus in the patients selected for the study ranged from 1 to 21 years.

TABLE : 4
SHOWS DISTRIBUTION OF DURATION OF DISEASE IN YEARS

Duration of disease	No. of patients	Percentage
≤ 5 years	44	29%
6-10 years	63	42%
11-15 years	21	14%
≥ 16 years	22	15%

CAUSE FOR DETECTION OF PATIENTS

The 150 patients in the study group had varying mode of presentation at the time of diagnosis.

The mode of presentations were the typical symptoms of diahetes mellitus like polyuria, Nocturia polydipsia, polyphagia, loss of weight and increased fatiguability.

Fever, which was due to respiratory and urinary tract infections and tuberculosis.

Few of them presented with symptoms suggestive of ketosis like abdominal pain, vomiting, nausea, altered sensorium and coma.

Other symptoms which includes pruritis valvae and balanophosthitis.

TABLE : 5
SHOWS THE PERCENTAGE OF DISEASE PRESENTATION

Symptoms	No. of patients	Percentage
Weight loss triedness Polyuria, polyphagia, polydispsia	65	44%
Fever due to respiratory and urinary tract infection	39	26%
Symptoms of ketosis	22	14%
Tuberculosis	9	6%
Others	15	10%

KETOSIS PRONENESS

The patients of type I diabetes mellitus are more prone to develop diabetic ketoacidosis.

Symptoms with which the patient may present include abdominal pain, nausea, vomiting, lethergy, altered sensorium and coma patient may present initially with symptoms of

ketosis or develop ketosis atleast once during their life time.

Ketoacidosis is one of the life threatening acute complication of type I diabetes mellitus, early and prompt diagnosis and management brings on a dramatic recovery.

HYPO GLYCEMIA

It is one of the most commonly occurring acute complication of type I diabetes mellitus.

Significant number of patient develop hypoglycemia during the course of illness, due to varying causes.

The patient may experience giddiness, sweating palpitations, tachycardia, altered sensorium drowsiness and even coma.

Prompt diagnosis and treatment is necessary.

Table 6 shows the number of patients who had acute complications.

TABLE : 6
SHOWS PREVALENCE OF ACUTE COMPLICATIONS

Acute complications	No. of patients	Percentage
Ketoacidosis	49	32%
Hypoglycemia	86	57%

FAMILY HISTORY OF DIABETES MELLITUS

In type I diabetes mellitus there is a significant family history. Out of 150 patients 20 had family history.

TABLE : 7
SHOWS VARYING DISTRIBUTION OF FAMILY HISTORY

Relatives	No. of patients	Percentage
Father	7	4.7%
Mother	5	3.3%
1st Degree	4	2.7%
2nd Degree	4	2.7%
Total	20	13.3%

Body mass index

BMI with calculated using the formula

BMI = weight in Kilograms Height in meter.

BMI (Body mass index)

17-25 is the normal range for women

17-24 is normal for men

<17 - under weight

25-30 over weight

>30 obesity

TABLE : 8
SHOWS THE BODY MASS INDEX OF THE STUDY GROUP

BMI	No. of patients	Percentage
Normal	118	78%
Under weight	19	13%
Over weight	13	9%
Other	-	-

PULSES

Among the 150 patients under my study, all the peripheral pulses were felt normally in 148 persons.

BLOOD PRESSURE

Out of the 150 patients 30 persons had systemic hypertension, with almost equal gender distribution. 14 males and 16 females hypertension may lead to increase in the incidence of microvascular complications like retinopathy, neuropathy and rephropathy, it also has a significant association with the macrovascular complications.

The Table shows No. 9 of patient considered to be hypertensive.

TABLE - 9

SHOWS THE PREVALENCE OF HYPERTENSION

No. of patients with HT		**Percentage**
Male	14	21%
Female	15	18%
Total	29	19%

Duration of Disease	**Total with Hypertension**			**Percentage**
	Male	**Female**	**Total**	
≤ 5	-	-	-	-
6 - 10	1	-	2	3.1%
11 - 15	4	6	10	47.6%
> 16	3	4	7	77%

NEUROPATHY

Diabetic neuropathy occurs in more than 50% of patients with diabetes both in type 1 and type 2.

TABLE - 10

SHOW THE PREVALENCE OF NEUROPATHY IN THE STUDY

Duration of Disease	No. of patients with neuropathy			Percentage
	Male	Female	Total	
≤ 5	1	2	3	7%
6 - 10	9	8	17	25%
11 - 15	5	6	11	52%
> 16	6	7	13	59%

A total of 44 persons had neuropathy with a p value of < 0.001 it is considered significant at 1% level.

RETINOPATHY

Diabetic retinopathy is estimated to be the most frequent cause of new cases of blindness in the persons in between the age group of 25 and 75.

Retinopathy is rare during the initial stage of the disease, as the duration of disease increase the chances of having retinopathy is more.

The prevalence of retinopathy in the study group is given in the table - 113 in which 25 of them had retinopathy.

TABLE - 11

Duration	No. of patients			Percentage
	Male	Female	Total	
≤ 5	1	0	1	2%
6 - 10	4	5	9	14%
11 - 15	5	6	11	52%
> 16	7	9	16	72%

A total at 37 persons had retinopathy value < 0.001, significant at 1% level.

NEPHROPATHY

Diabetes is the most common single disease causing renal failure progressing to end stage renal disease ESRD in both type 1 and type 2 diabetes mellitus.

A considerably higher fraction of them belong to type 1 disease.

TABLE - 12

SHOWS THE PREVALENCE OF NEPHROPATHY IN THE STUDY GROUP

Duration	No. of patients			Percentage
	Male	Female	Total	
≤ 5	-	-	0	-
6 - 10	1	1	2	3%
11 - 15	4	5	9	42%
> 16	7	7	14	63%

A total number of 25 persons has nephropathy p value 0.001, which in significant at 1% level.

DYSLIPIDEMIA

The increased prevalence of macro vascular disease is due to accelerated atherogenic potential in the diabetics, dyslipidemia play a significant role in Atherogenesis although type 1 disease contributes a smaller fraction when compared to type 2 disease.

Totally 14 persons had dyslipidemia.

4 persons had coronary artery disease which included :

3 Males and 1 Female

Peripheral vascular disease was detected in 2 persons both of them males.

Glycemic control.

In my study glycemic control was good in most of the 117 persons patients, i.e. <7% of HbAIc.

In 29 patients between 7 to 8

10 patients had HbA1c more than eight.

In my study 18 patients had microalbuminuria and 7 had clinical protienuria.

DISCUSSION

The onset of type 1 diabetes world wide most commonly occurs between the age of 10 - 14.

In my study 64 persons were detected to have type 1 DM in the age group 11 - 15, which constituted 42%.

In the age group of 16 - 20 there were 51 persons, 34%.

Prevalence of type 1 diabetes is common in males than in females, peak age of diagnosis was 11 for girls and it was between 11 - 18 for boys. The occurrence of disease was maximal at 11 years in urban group and 18 years in rural population Sridhar GR, Gender difference in Childhood diabetes, International Journal of Diabetes in Developing Countries - 1996.

In a study done at institute of child health, Sengottuvel et al., the incidence of Juvenile diabetes in the age group 11 - 15 yrs was 72.6%[28].

The incidence shows geographic variation with very low incidence at china and some parts of South America. Family history of diabetes was present in 20 patients (13%).

Positive history in father in 7 cases (4.7%). mother 5 - cases 3.3%).

In the EURODIAB survey the risk for a type 1 diabetic mother of having a child with diabetics before the age of five was 1.8% and for father 3.4%.

The usually reported figures are 6 - 8% for fathers 2-4% for mother 6 - 12% if both have diabetes clinical features at the time of diagnosis.

The most common presentation is rapid weight loss with polyuria, nocturia, polydipsia,

and overwhelming fatigue. In my study 65 patients had the above symptoms for which they were diagnosed to have type - 1 DM.

The next common mode of presentation was fever due to respiratory and urinary tract infection, 9 patients in my study has tuberculosis at the time of diagnosis.

If the diagnosis is not made at an early stage symptoms worsen, with development of abdominal pain, nausea, vomiting, dehydration and signs of acidosis.

In my study 22 patient were diagnosed to have of ketocidosis at the time of diagnosis.

Acute complications

Both acute and chronic complication reduce life span by 1/3 rd. Diabetic ketoacidosis continue to be the important cause of morbidity and 5-10% of mortality[29].

In my study 49 patient had at least one episode suggestive of ketoacidosis in which 22 patients had ketoacidosis at the time of diagnosis.

On enquiring the patients it was found that the patients were not taking treatment with insulin regularly.

Infection is an other important cause that precipitates ketoacidosis, myocardial infarction a minor role.

In about 40% of patients in a study of Birmingham UK, the precipitating factor could not be identified[30].

The incidence of ketoacidosis has decreased markedly in the recent past due to effective diagnosis and early management. There is also an increased awareness among type 1 diabetic

patients.

Hypoglycemia is an another important complication, It is a major factor in preventing the patients from achieving near normal glucose targets. Nocturnal hypoglycemia may cause death undisturbed in bed[31]. The much of the epidemiological data undertaken in 1980s showed hypoglycemic side effects of intensive insulin therapy.

In DCCT of those randomly assigned to standard insulin therapy, around 10% experienced at least one episode of hypoglycemia over a period of 12 months.

In my study 86 persons had at least one episode of hypoglycemia, which constituted about 57%.

Most of the patient had history of not taking food after insulin therapy. Few of them had a strenous workout or exertion.

The factor that precipitate hypoglycemia include over dosage, associated renal failure, rapid absorption, as in abdomen injection. Counter regulatory hormone deficiency which may occur following exercise or postpartum inadequate food intake and certain drugs (e.g pentamidine, salicylates, Beta Blockers).

Body mass index BMI was normal in 118 patient[19]. Of them were under weight and 13 over weight obesity plays a major role in type 2 DM only.

Hypertension is more common in diabetic people than in general population affecting 10 - 30%. of type 1[82] diabetic patient there are racial and ethnic difference in the prevalence of hypertension less common among native and Mexican Americans[33] Haffners mitchell B, Stern et al study proved this.

There is an increased association of hypertension with nephropathy in type 1 patients.

In my study 30 patients had hypertension which is about 20%. As the duration of disease increase the chance of getting hypertension is more. 65% of patient who has duration of more than 10 yrs developed hypertension with most of them having coexisting nephropathy.

Diabetic neuropathy occurs in both acute and chronic form. The prevalence of neuropathy was 52% in those over 10 yrs of disease and 59% in those over 15 Yrs of disease duration.

In Diamond study of complication (Diacomp) there was high icidence of neuropathy[34] 59% in Puerto Rico and in Eastern Europe. The EURODIAB IDDM complication study showed in Eastern Europe it was 46.4% with a mean duration of 14.2 years and north western europe 24.9%, mean duration 15.4 years.

Retinopathy is found in almost all individuals who have diabetes for > 20 years 25% incidence with 5 years and 80% incidence with 15 years of type 1 diabetes.

In my study there was gradual increase in retinopathy as the duration increase. It was 14% with a mean duration of 7 years. It is 52% with a mean duration of 13 years. In persons with duration more than 16 yrs the prevalence was 72.%.

The study show an association between Retinopathy and hypertension, Out of 31 persons with retinopathy 24 had hypertension. 6 persons with hypertension showed no evidence of retinopathy.

The annual incidence of diabetic nephropathy in type 1 reaches a maximum of 3% after 15 yrs and declines to less than 1% after 30 years[35] as observed by Andersen et al nephropathy

in type 1 diabetes an epidemiological study. The cumulative risk is 25 - 30%. Hanscn HP. Lund Rossing et al. my study showed diabetic nephropathy in 63% of patients with duration more than 16 years, the prevalence was 42% with a mean duration at 12.5 yrs.

The study included patient with both incipient and overt nephropathy, in which incipient nephropathy may revert to normal, or progress to overt nephropathy.

EURODIAB study did not demonstrate a great degree of variation. It showed a prevalence of 25% in those with ≤ 5 years of disease duration Diacomp study showed 55% in those with duration of 5 - 9 yrs.

In my study which had 25 patients with nephropathy 21 had hypertension. In some patients the AER remain normal even several years after diagnosis a study. Lind, Jensen Deckert[36] et al., showed this.

Another study showed 6 - 19% of microalluminuria in 1-5 years of disease duration warram, Gearin Latel et al.

Dyslipidemia with increased production of VLDL and TGL and decreased production of HDL occurs in diabetes. Dyslipidemia may lead on to macrovascular disease mainly CAD and priority must be given to prevent CAD. The study had 4 patients with coronary artery disease and 2 with peripheral vascular disease no one had CVA.

Good glycemic control, prevents the micro and macrovascular complications. Reduction of HbA1c by 1% reduces microvascular[38] complication by 37%, myocardial infarction by 14%, risk of death related to diabetes decreased by 21%.

A person with HbA1c of less then 7% is said to have good glycemic control, 7% A/c

correlates to 170 mg% and 8% to 205 mg%[39].

10 person with poor glycemic control had two or more microvascular complications.

24 person had moderate control and most of them had atleast one microvascular complications.

However that only one HbA1c measurement is unlikely to reflect glycemic control over long periods.

In my study 25 patients had micro albuminuria in which 17 had micro albuminuria and 7 marcoalbuminuria or clinical proteinuria. All these were categorised as having neprhopathy either incipient or overt nephropathy. Patients with microalbuminuria may progress to clinical proteinuria or revert back to normal.

However micro albuminuria may also occur in some other conditions which may include infection which where not excluded in the study.

There was not much significance in the prevalence of macrovascular complication, as the duration of is about 20 years only.

Although the study has showed the approximate prevalence of complication, move sophisticated investigation and appropriate clinical examination should be done to find the accurate prevalence rate of the complications.

CONCLUSION

Study population consisted of 150 type 1 diabetes patients selected randomly at Chennai.

* Age of diagnosis for most of them was between 11 - 15 years. 42% of the study group followed by 16 - 20 years, 34%.

* Initial mode of presentation was polyuria nocturia polydipsia polyphagia and excessive fatiguability and weight loss in majority of them 65 patients (44%) which formed 44% of the study population.

22 of the patients presented with ketoacidosis.

Tuberculosis as a complication of diabetes was found in 9 patients.

Acute complications like ketacidosis and hypolycemia were present in 49 and 86 patient respectively at least once in their life time.

Positive family history present in 20 patients.

Prevalence of microvascular compliaction and hypertension increases as the duration of disease is more.

Microvascular complication were found in patients with a prolonged disease duration combined with a poor glycemic control.

Retinopathy being more common with increased duration.

The prevalence of nephropathy and neuropathy is also high.

Complications	**No. of patient in the duration of disease 10-15 years**	**No. of patient in the duration of disease ≥ 16 years**
Hypertension	10 (47%)	17(77%)
Neuropathy	11(52%)	13(59%)
Retinopathy	11(52%)	16(72%)
Nephropathy	9(42%)	14(63%)

There was a co-existence of hypertension, retinopathy and rephropathy in most of the patient, with a longer duration of disease.

ABSTRACT

To study the prevalence of complications in type 1 diabetesmellitus and clinical feature of type 1 diabetes.

Randomly selected 150 patient who were diagnosed before 25 years of age were assessed by detailed history elicitation and clinical examinations laboratory analysis was done for renal function test including albuminuria and for glycemic control and non invasive investigation like Echo cardiogram, ultrasound and roentgenogram.

There is increased prevalence of micro vascular complication as the duration of disease increased.

There was also different mode of initial presentation, with coexistent findings of hypertension with microvascular complications.

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ABBREVIATION

DM	-	Diabetes mellitus
OGTT	-	Oral glucose tolerance test
WHO	-	World health organisation
HLA	-	Human Leucocyte antigen
LADA	-	Late onset diabetes in adults
CNS	-	Central nervous system
FFA	-	Free Fatty acids
DICA	-	Diabetic Ketoacidosis
IRMA	-	Intra retinal microvascular abnormality
ESRD	-	End stage renal disease
VLDL	-	Very low density lipoprotein
LDL	-	Low density lipoprotein
NEFA	-	Non esterified fatty acids
HT	-	Hypertension
CAD	-	Coronary artery disease
UTI	-	Urinary tract infection
BMI	-	Body man index
HDFP	-	Hypertension detection and followup programme
MNSI	-	Michigan neuropathy screening instrument
CVAT	-	Cerebrovascular accident

KEYS

F/H	-	Family history
BMI	-	Body mass index
1	-	Normal weight
2	-	Under weight
3	-	Over weight
CAD	-	Coronary artery disease
PVD	-	Peripheral vascular disease

Glycemic Control

1	-	Good
2	-	Optimum
3	-	Poor

Urine albumin

N	-	Normal
MA	-	Micro albuminuria
CP	-	Clinical proteinuria
+	-	Present
–	**-**	**Absent**

PROFORMA

CLINICAL FEATURES OF TYPE 1 DIABETES MELLITUS AND PREVELANCE OF ITS COMPLICATIONS

Name :

Age :

Sex :

IP / OP Number :

Address :

HISTORY

1. Age of diagnosis :
2. Cause for detection :
3. Ketosis proneness :
4. Hypoglycemia proneness :
5. Duration :
6. Family history of diabetes :
7. Obstetrics history :
8. Smoking :
9. Alcoholism :

PHYSICAL EXAMINATION

1. Height

2. Weight

3. Body Mass Index

4. Pulse Right Left

   Carotid
   Brachial
   Radial
   Femoral
   Pepliteal
   Posterial tibial
   Dorsalis pedis

5. BP

   Lying
   Standing

6. Thyroid enlargement

7. Balanoposthitis

8. Cardiovascular system

9. Respiratory system

10. Abdomen

11. Neurological

    Higher functions
    Cranial nerves
    Motor system
        Deep tendon reflex
        Sensory
            Pain, touch, temperature
            Vibration, joint position

12. Fundoscopy

INVESTIGATIONS

1. Plasma glucose F/PP
2. Urine sugar
3. Microalbuminuria / clinical protenuria
4. Urine acetone
5. Blood urea
6. Serum creatinine
7. Serum electrolytes

   Na^+
   K^+
   HCO_3
   $C1^-$

8. Lipid profile

   Total cholesterol
   Triglycerides
   HDL
   LDL
   VLDL

9. Glycosylated Haemoglobin A1c
10. Chest X-ray PA view
11. ECG

Ultrasonogram